Biological Markers for Chemotherapy Induced toxicities in Patients with Malignancy

Thesis

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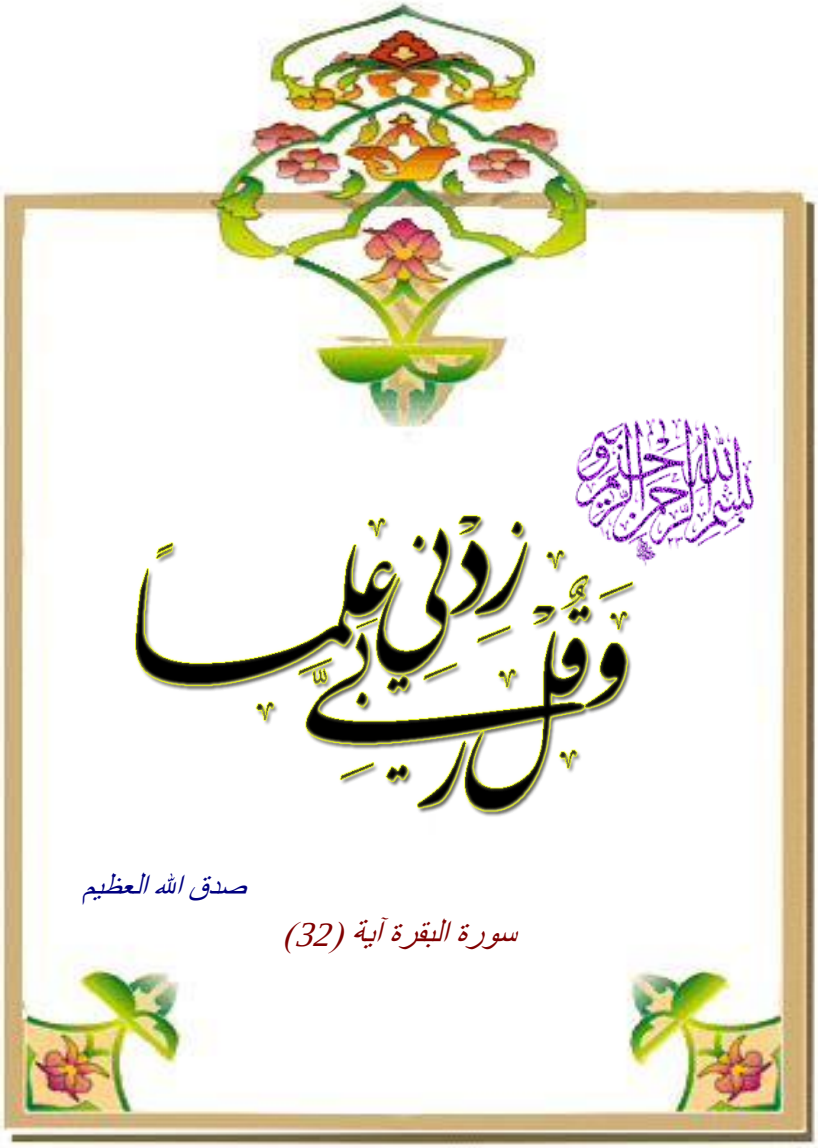

صدق الله العظيم

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Rasha Adel Fathy Thabet

Contents

List of Abbreviations

5-FU	:	5 fluorouracil
ADE	:	Cytarabine, daunorubicin, etoposide
ADRs	:	Adverse Drug Reactions
AEL	:	Acute erythroid leukemia
AIE	:	Cytarabine, idarubicin, etoposide
ALCL	:	Anaplastic large cell lymphoma
ALL	:	Acute lymphocytic leukemia
allo-SCT	:	Allogeneic stem cell transplantation
ALT	:	Alanin aminotransferase
AMKL	:	Acute megakaryocytic leukemia
AML	:	Acute myelogenous leukemia
AMML	:	Acute myelomonocytic leukemia
AMoL	:	Acute monocytic leukemia
APL	:	Acute promyelocytic leukemia
AST	:	Aspartate aminotransferase
AVN	:	Avascular necrosis
BFM	:	Berlin-Frankfurt-Munster group
BMI	:	Body mass index
BUN	:	Blood Urea Nitrogen
CAD	:	Coronary Artery Disease
CBC	:	Complete Blood Count
CML	:	Chronic myelogenous leukemia

List of Abbreviations (Cont.)

CNS	:	Central Nervous System
CPM	:	Cyclophosphamide
CRT	:	Cranial radiotherapy
CT	:	Computarized Tomography
DLBCL	:	Diffuse large B-cell lymphoma
DNA	:	Deoxiribonucleoprotein
EBV	:	Epstein-Barr virus
ECHO	:	Echocardiography
EFS	:	Event-free survival
ER	:	Endoplasmic reticulum
ESAs	:	Erythropoiesis stimulating agents
FAB	:	French-American-British
FISH	:	Fluoresence in situ hybridization
GCSF	:	Granulocyte colony stimulating factor
GFR	:	Glomerular filtration rate
GH	:	Growth Hormone
GI	:	Gastrointestinal
GLP-2	:	Glucagon-like peptide-2
GnRH	:	Gonadotropin Releasing Hormone
GvHD	:	Graft-versus-host disease
GvL	:	Graft-versus-leukemia
HAM	:	High-dose cytarabine and mitoxantrone

List of Abbreviations (Cont.)

Hb	:	Hemoglobin
HD ara-c	:	High-dose cytosine arabinoside
HF	:	Heart Failure
HRS	:	Hodgkin-Reed-Sternberg
HSCT	:	Hematopoietic stem cell transplants
IFN-α	:	Interferon α
IL-6	:	Interleukin 6
JMML	:	Juvenile myelomonocytic leukemia
LCLs	:	Large cell lymphomas
LVEF	:	Left Ventricular Ejection Fraction
MAbs	:	Monoclonal antibodies
MI	:	Myocardial infarction
MPO	:	Myeloperoxidase
MSC	:	Mesenchymal stem cells
MTX	:	Methotrexate
MVC	:	Micro vessel count
NB	:	Neuroblastoma
NCI	:	National Cancer Institute
NE	:	Neutrophil
NHL	:	Non Hogkin Lymphoma
NPY	:	Neuropeptides-Y
NRSTSs	:	Nonrhabdomyosarcoma soft tissue sarcomas

List of Abbreviations (Cont.)

OS	:	Overall survival
PCR	:	Polymerase chain reaction
PLT	:	Platelet
Rb	:	Retinoblastoma
RBS	:	Randam Blood Sugar
RNA	:	Ribonucleoprotein
ROC	:	Receiver-operating characteristic
RT	:	Radiotherapy
SCT	:	Stem cell transplantation
SMNs	:	Second malignant neoplasms
SVC	:	Superior vena cava
TG	:	Triglyceride
TLC	:	Total Leucocytic Count
TNF-α	:	Tumor Necrotic Factor α
TnI	:	Troponin I
TPO	:	Thrombopoietin
VBL	:	Vinblastine
VCR	:	Vincristine
VEGF	:	Vascular endothelial growth factor
VRL	:	Vinorelbine
WBC	:	White blood cell count

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Introduction

Chemotherapy is an important primary and adjuvant therapy for cancer patients. The cytotoxicity of antineoplastic agents affects not only tumor cells but also rapidly proliferating normal cells **(Hirotani et al., 2006).**

Severe adverse drug reactions (ADRs) are a major issue for drug therapy because they can cause serious disorders and be life-threatening. Many severe ADRs appear to be idiosyncratic and unpredictable. Genetic factors may underlie susceptibility to severe ADRs, and identification of predisposing genotypes may improve drug therapy by facilitating prescreening of carriers for specific genetic biomarkers **(Tohkin et al., 2010).**

Advances in molecular biology and genetics over the past 60 years have facilitated development of multiple chemotherapeutic agents that are active against most common malignancies. However, significant heterogeneity in the efficacy and toxicity of these agents is consistently observed across human populations. **(Miller and Howard 2007).**

The spectrum of cardiac side-effects of cancer chemotherapy has expanded with the development of combination, adjuvant and targeted chemotherapies. Their

administration in multiple regimens has increased greatly. Cardiac toxicity of anthracyclines involves oxidative stress and apoptosis. High doses of the alkylating drugs cyclophosphamide and ifosfamide may result in a reversible heart failure and in life-threatening arrhythmias. Myocardial ischemia induced by the antimetabolites 5-fluorouracil and capecitabine impacts prognosis of patients with prior CAD. Severe arrhythmias may complicate administration of microtubule inhibitors **(Monsuez et al., 2010).**

Mesenchymal stem cells (MSC) are important cellular component of the bone marrow microenvironment in supporting hemopoiesis. MSCs are resistant to chemotherapy commonly used in hematologic malignancies but are relatively sensitive to anti-microtubule agents. However, the response of MSCs to other chemotherapeutic agents commonly used in solid tumour settings remains unknown **(Li et al., 2010).**

Common complications of chemotherapy thus include stomatitis and enterocolitis. Methotrexate (MTX) is an antimetabolite drug that blocks the production of biologically active forms of folic acid. The major lesions resulting from its cytotoxic effects occur in bone marrow and the intestinal tract **(Hirotani et al., 2006).**